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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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RADIOACTIVE NEW DRUGS AND RADIOACTIVE BIOLOGICS

Notice of Proposed Rulemaking

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 1, 310, 312, 370]

RADIOACTIVE NEW DRUGS; RADIOACTIVE BIOLOGICS

Notice of Proposed Rule Making

An order was published in the FEDERAL REGISTER of January 8, 1963 (28 FR 183), in which the Commissioner of Food and Drugs exempted, until further notice, radioactive new drugs (radiopharmaceuticals and radioactive biologics) for investigational use from the requirements of § 312.1 (21 CFR 312.1), provided they are being shipped in complete conformity with the regulations issued by the Atomic Energy Commission in Title 10, Parts 30 through 36, of the Code of Federal Regulations.

For the convenience of the reader, the former designations of sections in Title 21 which were recodified in the FEDERAL REGISTER on November 20, 1973 (38 FR 32048), and March 29, 1974 (39 FR 11680), and which are referred to in this proposal are as follows:

Recodified as:	*Formerly—*
§ 310.102	§ 130.37
§ 310.503	§ 130.49
§ 312.1	§ 130.3
§ 314.1	§ 130.4
Part 601	Part 273
§ 601.2	§ 273.201

The purpose of the temporary exemption granted by the January 1963 order was to allow for the continued availability of these unique new drugs while the Federal agencies responsible for supervising these drugs explored ways to avoid unnecessary duplication of regulatory controls. The exemption applied only to radioactive drugs manufactured from reactor-produced radionuclides, which are the only radioactive drugs subject to the regulatory controls of AEC. Because AEC has no regulatory control over radioactive drugs manufactured from non-reactor-produced radionuclides, these have never been exempt from the requirements of § 312.1.

This exemption was revoked in part by an order published in the FEDERAL REGISTER of November 3, 1971 (37 FR 21026) in which the Commissioner added a new § 310.503 to Title 21 of the Code of the Federal Regulations. This new section listed specific reactor-produced isotopes which, for certain stated uses, were no longer exempt from § 312.1. After further review of the 1963 exemption, it is the opinion of the Atomic Energy Commission and the Food and Drug Administration that all radioactive drugs should now become subject to the same clearance procedures as other drugs under section 505 of the Federal Food, Drug, and Cosmetic Act and 21 CFR 312.1 and 314.1; and section 351 of the Public Health Service Act and 21 CFR 601.2. The exemption from § 312.1 which now exists for some radioactive new drugs for investigational use is no longer justified or in the public interest.

On July 17, 1974, the Atomic Energy Commission published in the FEDERAL REGISTER (39 FR 26143) a final order modifying its procedures for licenses regarding radioactive materials for medical use. As a condition for investigational use of certain radioactive materials in human beings under a group license, AEC will require the licensee to be covered by a "Notice of Claimed Investigational Exemption for a New Drug" which has been accepted by FDA. Further, AEC will require, as one precondition to becoming licensed to manufacture or distribute radioactive drugs for medical uses under group licenses, evidence that the applicant has complied with the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act, as applicable. This order eliminates any duplication or overlapping between AEC and FDA on matters of controlling the pharmaceutical quality of radioactive drugs and the safety and effectiveness of all radioactive drugs with respect to the patient. This aspect of the AEC order is effective on January 13, 1975.

Accordingly, the Commissioner proposes to revoke his order of January 8, 1963, and classify, by use, radioactive drugs either as "new drugs" or as generally recognized as safe and effective for their intended use and therefore not "new drugs." All radioactive "new drugs" will be subject to the requirements of the new drug and investigational drug provisions of the Federal Food, Drug, and Cosmetic Act and the licensing provisions of the Public Health Service Act. Any radiopharmaceutical which is not a "new drug," i.e., when used under the conditions specified, will require neither an IND nor an NDA, but will require certain documentation to establish that the drug is in fact being used under the conditions set forth in the regulations. Similarly, use of any radioactive biologic under the specified conditions shall constitute licensure, and no other product license shall be required.

Because of the effective date of the AEC order and the need for FDA regulations to be in force by that date, the Commissioner's proposal identifies effective dates for specific changes. The Commissioner intends to issue a final order on this subject matter with effective dates as proposed. Therefore, all interested persons should file comments within the time allotted. No extension of time for filing of comments will be made.

A. *Effect of revocation of 1963 exemption.* The proposed addition of paragraph (h) to § 310.503 and deletion of the "Note" at the end of § 312.1 are intended to revoke the Commissioner's exemption order of January 8, 1963. Upon revocation of this exemption, the Food and Drug Administration will be responsible for assuring the safety and effectiveness of all radioactive drugs, regardless of the source (reactor, accelerator, or naturally occurring) of the radionuclide contained in it. Beginning January 1, 1975, no person shall introduce into interstate commerce a radioactive drug, except those covered by paragraphs B, C, and D of this preamble, unless it is subject to a "Notice of Claimed Investigational Exemption for a New Drug" (IND) or an approved new drug application (NDA) or product license application. Any IND or NDA shall be submitted in accordance with 21 CFR 312.1 or 314.1. A product license application for a biologic shall be submitted in accordance with 21 CFR Part 601.

Placing radioactive drugs under new drug procedures will necessitate certain changes in the IND application forms. Because radioactive drugs differ from other drug products in that radiation is usually the primary safety consideration, the Commissioner proposes to amend § 312.1 to require for such drug products sufficient information to permit adequate calculation of radiation dosimetry prior to human use. Accordingly, item 6 of Form FD–1571 "Notice of Claimed Investigational Exemption for a New Drug" would be altered to reflect this requirement for a radioactive new drug. Also, item 10.a of Form FD–1571 would be amended to require that during phase 1 of the clinical studies there shall be evaluation of radionuclide excretion, whole body retention, and organ distribution so that dosimetry calculations may be refined on the basis of adequate information from human use.

The Commissioner recognizes that radioactive drugs are often administered at very low pharmacologic doses and for short periods of time. In these cases chronic toxicity studies may not be required. In addition, both acute and chronic pharmacologic toxicity may be evaluated using a nonradioactive, chemically identical form of the agent to be studied. In certain cases, for example, when the radioactive drug consists of a small quantity of a normal body constituent in water or saline, animal toxicity studies may not be required. None of these special circumstances are in conflict with the regulations, which require only, as stated in item 6.a of Form FD–1571, that there be "Adequate information, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug."

B. *Transitional regulation of certain radioactive drugs with "well-established medical uses."* Section 310.503, established by the Commissioner in the order published in the FEDERAL REGISTER of November 3, 1971 (37 FR 21027), listed specific reactor-produced radionuclides ("isotopes" in the order) which, for the uses stated, were no longer exempt from § 312.1. The radioactive drugs listed in § 310.503 were those which the Atomic Energy Commission determined had well-established uses and for which the Atomic Energy Commission, the Division of Biologic Standards of the National Institutes of Health, and the Food and Drug Administration considered that manufacturers and distributors may reasonably be expected to submit adequate evidence of safety and effectiveness for use as recommended in appropriate labeling. The agencies also concluded that these drugs should not be distributed under investigational use labeling when actually intended for use in medical practice. After the effective date of the order, March 3, 1972, shipment or other delivery of these radioactive drugs has been

permitted only under the investigation requirements of § 312.1 including the filing of an IND, or under an approved NDA pursuant to § 314.1, or under a product license pursuant to § 601.2.

In order to prevent any disruption in the availability of these medically important radioactive drugs during the transition from "exempt status" to "regulated status," the Commissioner provided as follows: Each manufacturer and distributor was given until March 3, 1972, to submit an NDA, application for product license, or IND for each radioactive drug containing a listed radionuclide ("isotope") for a listed purpose for which the manufacturer or distributor did not have an approved NDA or product license in effect. Commercial distribution of those drugs for which an NDA or product license application had been submitted by March 3, 1972, was permitted without approval of the NDA or product license application until the manufacturer was notified otherwise by the Food and Drug Administration. A number of new drug applications and applications for product license for these radioactive drugs were filed pursuant to § 310.503 and are currently being reviewed by the Food and Drug Administration.

The Commissioner anticipates that nearly all of the radioactive drugs now listed in § 310.503, including all of those which are widely used in the practice of nuclear medicine, will shortly be the subject of approved new drug applications or product licenses.

Therefore, the Commissioner proposes to amend § 310.503 by revising paragraph (d) so that, if a manufacturer or distributor had submitted an NDA or application for product license or an IND for a radioactive drug by March 3, 1972, as provided in § 310.503, then that manufacturer or distributor may continue to ship that radioactive drug in interstate commerce until the Food and Drug Administration denies the NDA or product license application or terminates the IND, or until Judy 1, 1975, whichever occurs first. This proposal, if adopted, will establish July 1, 1975, as the final date by which all radioactive drugs now covered by § 310.503 must have an approved NDA or product license if they are to be introduced into interstate commerce.

Subsequent to the November 3, 1971 order revoking the exemption from new drug requirements for certain radioactive drugs, the Atomic Energy Commission identified other radioactive drugs which it considered also had well-established medical uses. The Commissioner has reviewed this list and concludes that manufacturers and distributors of these drugs also may reasonably be expected to submit adequate evidence of safety and effectiveness for use as recommended in appropriate labeling. These drugs should not be distributed under investigational use labeling when actually intended for use in medical practice.

Therefore, the Commissioner proposes that § 310.503 be amended by adding a new paragraph (f) to list new radionuclides ("isotopes") which, if contained in a drug and intended for a listed purpose, should be covered by an NDA or product license. If any person believes other radioactive drugs are widely used in medical practice and should be added to this list, he is invited to submit comments and data proposing and justifying the addition of such drugs.

In order to prevent any interruption in the availability of these previously exempted radioactive drugs, special transitional steps similar to those used in the November 3, 1971, order are proposed. Manufacturers and distributors will be given until December 31, 1974, to submit an NDA, application for product license, or IND for each drug containing any of these radionuclides ("isotopes") and for a purpose listed for which the manufacturer or distributor does not have an approved NDA or product license in effect. After December 31, 1974, shipment or other delivery of these radioactive drugs will be permitted only under the investigational requirements of § 312.1, including the filing of an IND, or under an approved NDA pursuant to § 314.1, or under a product license pursuant to § 601.2, except for those for which an NDA or product license application is submitted on or before December 31, 1974. Commercial distribution of those drugs for which an NDA or product license application is submitted by December 31, 1974, will be permitted for a reasonable period of time without approval of the NDA or product license. It is impossible to predict now what length of time will be reasonable, because it is not know how many applications will be submitted or what difficulties may arise after their submissions.

The Commissioner proposes to permit the affected radioactive drugs to be shipped in interstate commerce either until the Food and Drug Administration denies the NDA or product license application or until July 1, 1975, whichever occurs first. The Commissioner will, however, extend the cutoff date beyond July 1, 1975, if, after all applications are received, i.e., after January 1, 1975, it appears that the period is unreasonably short.

C. *Transitional regulation of radioactive drugs for investigational use.* While the exemption of January 8, 1963, is in effect, investigational use of radioactive drugs (except those affected by the November 3, 1971, revocation) is not subject to the requirements of § 312.1, but rather to requirements of the regulations of the Atomic Energy Commission (10 CFR 35.11). In order to prevent interruption in on-going research studies when the exemption is revoked, the Commissioner proposes, in new paragraph (g) of § 310.503, to extend the exemption until July 1, 1975, for any use which has been approved, on or before October 1, 1974, as part of a study in accordance with the requirements of the Atomic Energy Commission or an Agreement State, if the manufacturer of the drug or sponsor of the investigation submits to the Food and Drug Administration certain information regarding the study. Any use which has not been approved prior to October 1, 1974, even though the research project had been previously approved, e.g., where a protocol is amended after October 1, 1974, to utilize a radioactive drug in a way not originally planned, must be in accordance with the requirements of § 312.1 including the filing of an IND.

D. *Treatment of radionuclides for certain research uses.* Tracer quantities of certain radionuclides are attached to various compounds in order to study drug metabolism, specific physiologic or pathophysiologic processes in humans, and the kinetics, distribution, and localization of the various "tagged" compounds. Such studies may not be related primarily to the health needs of the subjects involved but they are of established importance in the advancement of medical knowledge. The radionuclides may be produced by reactor or accelerator or may be naturally occurring.

The Commissioner proposes to determine that under the following circumstances the use of tracer amounts of radionuclides for these research purposes is generally recognized as safe and effective and that the drugs used in such studies will be considered not to be "new drugs" under section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)). Because of this determination, a researcher will not be required to comply with § 312.1 and specifically will not be required to file an IND in conjunction with research done under the conditions prescribed:

1. The drug must be administered at a dose that is pharmacologically inactive.

As a rule, studies of these types utilize drug dosages below the level at which pharmacologic activity, including adverse reactions, is produced. When a drug is used at such dosage levels, it poses no hazard measured in terms of traditional pharmacology. Therefore, the Commissioner finds that when radioactive drugs are administered in amounts which have been demonstrated not to produce clinically detectable pharmacologic activity in human beings, such drugs are and must be generally recognized as safe from the viewpoint of traditional pharmacology. The Commisisoner proposes that this demonstration be by reference to published literature regarding human experience or other prior valid human studies.

If neither published literature regarding human experience nor other prior valid human studies are available from which the threshold of pharmacologic activity of a specific drug may be determined, even the smallest amount of that drug must be assumed to produce pharmacologic activity. Therefore, that drug when administered in any amount cannot be determined to be generally recognized as safe; the drug is considered to be a new drug and any research with it must meet the requirements of § 312.1, including filing an IND.

The Commissioner is concerned, however, that the proposed standard for demonstrating the absence of pharmacologic activity may be unnecessarily

difficult to meet. The objective of the standard is to establish a test which will assure that no subject is at risk of a toxic reaction; at the same time, the test should not be needlessly burdensome. It is not expected that there will always have been a formal dose-response study that will permit precise definition at a lower limit of pharmacologic activity. This appears to be especially likely for some common substances that occur naturally in the body. The phrase "human experience" is intended to encompass both true dose-response studies and investigations which define such parameters as the usual blood level of a substance, and which may also define dose levels which would not be pharmacologically active. The Commissioner specifically invites comments on the appropriateness of the standard proposed and welcomes suggestions for alternative tests.

In this regard, the Commissioner has considered an alternative test, namely, that the amount administered not exceed 10 percent of the lowest single dose recommended on the labeling, or if the drug has no approved labeling, 10 percent of the lowest single dose recommended by recognized medical texts, with the exact dosage being reviewed by a peer committee for safety. That committee would assure that the dosage could not be reduced without jeopardizing the quality of the study and was justified by the information sought. The Commissioner finds this test has merit, but notes that certain drugs cannot be generally recognized as safe even at this low dose level, e.g., certain drugs used in treatment of neoplastic disease. Thus, to adopt this test of pharmacologic safety, the safety of each drug or drug class would have to be established individually on the basis of published literature in order for the Commissioner to find that the drug is generally recognized as safe for use under the conditions set forth. This creates serious difficulties concerning the feasibility of adopting this test at this time, although the test might well serve in the future for specified classes of drugs, e.g., substances which are naturally occurring in the human body.

The Commissioner has also considered allowing the demonstration of pharmacologic inactivity to be by reference to animal data. However, the Commissioner believes that prior human experience is essential for determining safety for use in human beings. The first clinical studies on any drug must be done under the requirements of § 312.1, including the filing of an IND. Thus, animal data alone cannot be used to demonstrate the threshold of pharmacologic activity in human beings.

2. Radiation exposure may not exceed AEC limits for occupational radiation workers.

When a pharmacologically inactive amount of a radioactive drug is used, the issue of safety for use in human subjects becomes primarily one of whether the exposure of a human subject to the amount of radiation involved is justified by the quality of the study being undertaken and the importance of the information it seeks to obtain.

Radiation exposure has been extensively studied in the last 3 decades. Published literature documents the procedures for calculating dosimetry, including radionuclide excretion, whole body retention, and organ distribution. Various organizations (including the Atomic Energy Commission, the Federal Radiation Council, the National Council on Radiation Protection and Measurements, the International Commission on Radiological Protection, and the United Nations Scientific Committee on the Effects of Atomic Radiation) have studied the maximum safe radiation exposures, on a single basis and on a cumulative basis, to human beings. A consensus has developed in the literature permitting the establishment of exposure levels which are acceptable from the standpoint of radiation safety. A selected bibliography regarding these matters is on file with the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, and may be seen during working hours, Monday through Friday.

The Atomic Energy Commission has established under 10 CFR 20.101 and 20.102 basic radiation protection criteria, including the specification of the maximum dose for single occasion exposures or maximum cumulative dose for multiple exposures per calendar quarter for occupational radiation workers. The criteria have been operational throughout the United States for over 15 years. The Commissioner believes that these criteria provide a reasonable basis for making an initial determination that a radioactive drug, when administered in amounts below the maximum quarterly dose for occupational radiation workers, is generally recognized as safe. These criteria enable a potential research subject, in research described above, to make an informed decision regarding participation in the study because he will, in effect, be deciding whether or not to become a radiation worker for the duration of the study.

The upper radiation limit for purposes of determining that a radioactive drug is not a "new drug" in no way suggests that any study within that limit is satisfactory. Each study must be useful and well designed, and radiation exposure involved must be reduced to the minimum necessary for the investigation. Similarly, the choice of an upper radiation limit for purposes of determining general recognition of safety is not to be construed as a Food and Drug Administration guideline regarding the upper radiation limit for an acceptable study under an IND, nor a lower limit below which no IND is required. The limit is solely for the purposes of determining that radioactive drugs, when administered in doses too small to produce a pharmacologic effect and below the radiation level set, and in a study approved and supervised as outlined below, are not "new drugs" under the act.

The Commissioner emphasizes that the criteria provide a basis for initially determining that a radioactive drug is generally recognized as safe. The Commissioner fully agrees with the following statement by the National Council on Radiation Protection and Measurements, in "Basic Radiation Protection Criteria" (Report No. 39, p. 14, 1971):

> It should be noted that each proposed human research application must be judged on its merits after review by competent peers, and the dose-limiting recommendations for radiation workers or the public do not apply to [human subjects] to be irradiated. Depending on circumstances, larger or smaller limits would be indicated.

The ultimate determination of safety rests on whether the amount of radiation exposure is necessary for the success of the study, and if so, is justified by the quality of the study and by the significance of the information sought.

3. The investigation must be approved and supervised by an appropriate peer review group.

Until the present time, the question of whether a given study is safe and justified has been considered in the context of each proposed study by at least one of three different groups: (i) The Atomic Energy Commission, through its expert panels; (ii) the reviewing bodies of the Atomic Energy Commission Agreement States; and (iii) the Radiation Safety Committees of so-called "Broad License Institutions" (committees which have met standards set by the Atomic Energy Commission and which are thereby empowered by the Commission to review investigational radionuclide uses). The experience of the Atomic Energy Commission has been that these different groups, all of which are basically "peer review groups," have reviewed individual studies with proper attention to such matters as informed patient consent, the quality of study and the usefulness of the information being sought, and the actual dose of radiation received by various parts of the body under the conditions of the study. Based upon the experience of the Atomic Energy Commission, the Food and Drug Administration proposes to establish standards under which new peer committees can be created to review, approve or disapprove, and monitor research studies involving radioactive drugs. The Commissioner, upon evaluation of the experience of the Atomic Energy Commission with "peer review committees" and the new requirements proposed herein for such committees, proposes to find that radioactive drugs, when administered within the dosage limitations and in types of research studies described in section D. of this preamble, and with prior approval and close scrutiny of "peer review groups" operating in accordance with proposed FDA-established standards, are generally recognized as safe from the viewpoint of radiopharmacology.

The effectiveness of radioactive drugs, when administered within the pharmacological and radioactive dosage limit described, under proper peer evaluation and supervision, is amply documented. "Effective," in this instance, means that such radioactive drugs, as used in these

investigations, provide valuable and important information which is not readily available without use of the radioactive drugs. A selected bibliography regarding effectiveness is on file with the Hearing Clerk, Food and Drug Administration, and may be seen during working hours, Monday through Friday. The proper functioning of the peer review groups assures that each study is useful, well designed, and likely to yield information of benefit to the scientific community, and that the radiation exposure cannot be reduced without jeopardizing the investigation. Thus, the Commissioner proposes to find that radioactive drugs, when used under the conditions described, are generally recognized as effective.

In summary, based upon extensive published literature concerning research with "tagged" radioactive drugs and exposure risks for occupational radiation workers, and upon the absence of a known safety problem apart from the potential hazard of radiation exposure, and upon the experience of the Atomic Energy Commission with peer review of research studies conducted under its auspices, the Commissioner proposes to conclude that these drugs are generally recognized as safe and effective when used in the types of research defined above under certain highly controlled circumstances. Therefore, under certain specified circumstances including (i) that the amount of the active drug administered be known not to cause any clinically detectable pharmacologic effect in human beings, (ii) that the amount of radiation exposure may not exceed the maximum exposure limits for occupational radiation workers, and (iii) that the investigation be approved and supervised by a peer review group operating in accordance with Food and Drug Administration regulations, drugs tagged by radionuclides in tracer quantities and used in the types of research defined above will be considered not to be "new drugs" under section 201(p) of the act (21 U.S.C. 321(p)).

The detailed conditions under which the radioactive drugs will be so considered are set forth in the proposed § 370.100. Such radioactive drugs used outside such conditions are not determined to be generally recognized as safe and effective and are therefore "new drugs" under section 201(p) of the act (21 U.S.C. 321(p)). Submittal of an IND will be required if the study deviates from these conditions, e.g., an investigation involving a radioactive drug which is given at a pharmacologically active dose or is above the radiation exposure limit, or an investigation involving a radioactive drug which meets the dosage limits set, but is not conducted under review of an FDA-approved Radiation Safety Committee.

The proposed determination that radioactive drugs are not "new drugs" for certain basic research uses does not include the research intended to demonstrate the clinical effectiveness of any drug, i.e., the so-called "clinical trial." The Commissioner wishes to make it clear, however, that a study is not excluded merely because it has potential clinical relevance. Thus, the initial investigations that demonstrate the localization of a drug in a particular organ or fluid space and determine the kinetics of that localization should be considered basic research. In contrast, the evaluation of the drug as a clinical tool, including comparison with other agents, should be considered as part of a clinical trial and subject to the requirements of § 312.1.

The proposed determination regarding new drug status does not alter the requirement under § 312.1 that every study, including any radioactive tracer study, conducted as part of the evaluation of any drug under that section, shall be carried out in compliance with that section rather than pursuant to proposed § 370.100.

The Food and Drug Administration may review any specific research study at any time to determine that it is within the purposes and restrictions of § 370.100. If it is found that a research project uses a radioactive drug for a purpose or in any way that is not encompassed in the Commissioner's findings that such drug is generally recognized as safe and effective, the Food and Drug Administration will take necessary steps to assure compliance with the act.

The proposed § 370,100 contains the criteria under which a radioactive drug will be considered not to be a "new drug" or under which a radioactive biologic will be considered licensed. These are (i) that an FDA-approved Radiation Safety Committee review the proposed study and make certain determinations regarding its safety and merit; (ii) that the amount of pharmaceutical ingredients administered be demonstrated not to cause a clinically detectable pharmacologic effect in human beings; and (iii) that the amount of radioactivity to which the patient is exposed be the minimum amount practicable for the study and in no event exceed the currently permitted occupational exposure limits for the radionuclide. A Radiation Safety Committee must meet certain standards regarding membership, and must agree to comply with Food and Drug Administration regulations, before obtaining Food and Drug Administration approval. Once approved, the Radiation Safety Committee, in approving individual studies, must assure that each study satisfies certain specified requirements, including qualifications of investigators, selection and consent of human research subjects, quality controls for the radioactive drug, standards for the research protocol, and monitoring of adverse reactions. These requirements are all contained in the proposed § 370.100. The Food and Drug Administration will permit each Radiation Safety Committee to develop its own working relationship with the Institutional Review Committee in the same institution. The Radiation Safety Committee may serve as a subcommittee of an Investigational Review Committee, or operate independently. The Food and Drug Administration will also permit a Radiation Safety Committee to perform functions required by the Atomic Energy Commission and appropriate State and local officials responsible for licensing persons engaged in possession and use of radioactive drugs.

The proposed § 370.100 also contains specific requirements regarding the label and labeling for a radioactive drug intended for use pursuant to the section. Because of the closely circumscribed conditions for use set forth in the section, the Commissioner finds that the requirements of section 502(f)(1) of the act regarding inclusion of adequate directions for use on the labeling are not necessary for the protection of the public health. Therefore, the proposed § 370.100 and the proposed amendment to § 1.106 as a cross-reference to § 370.100, include an exception from section 502(f)(1) of the act if certain other requirements are met. These requirements, taken together with requirements imposed by sections 502 (b) and (e) of the act, will mean that all labels and labeling must contain (i) the established name of the drug, if any; (ii) the established name and quantity of each active ingredient; (iii) the name, quantity and half-life of the radionuclide; (iv) the name and address of the manufacturer, packer or distributor; (v) the net contents; (vi) an identifying lot or control number; (vii) a prescription legend; and (viii) a statement reading "To be administered in compliance with the requirements of Federal regulations for radioactive drugs for research use (21 CFR 370.100)". Furthermore, if the drug is intended for parenteral use, the label shall contain a statement as to whether or not the drug is sterile. The other label and labeling requirements of section 502 of the act remain in force, where applicable. The Food and Drug Administration will also permit the label and labeling to contain information required by the Atomic Energy Commission or by State authorities who regulate radioactive materials.

At this time the Commissioner is not proposing any additional regulations pertaining to current good manufacturing practices regarding radioactive drugs, or additional reports to be filed by manufacturers of such drugs. These matters remain under study and will be handled in a subsequent proposal.

E. *Relationship between regulation by the Food and Drug Administration and licensing for use of reactor-produced materials by the Atomic Energy Commission and Agreement States.* The Atomic Energy Commission, under authority of the Atomic Energy Act, and in order to ensure the safe handling of radioactive materials, will continue to license, directly or in cooperation with the States, persons engaged in the possession, use, or transfer of reactor-produced radionuclides including radioactive drugs. A number of States, under working agreements with the Atomic Energy Commission under Federal law, license persons engaged in the possession, use, or transfer of reactor-produced radionuclides in their respective States. The Atomic Energy Commission retains responsibility for licensing such persons in those States where no such working agreements exist.

In order to avoid duplicative requirements by FDA and AEC in licensing of persons engaged in the manufacture and distribution of reactor-produced radioactive drugs, the Atomic Energy Commission and a number of States have agreed that they will use, as one precondition for licensing such a person, evidence that an IND concerning use of a radioactive drug by such person has been accepted by the Food and Drug Administration or that the Food and Drug Administration has approved an NDA or product license application submitted by such person concerning the radioactive drug. In the event that the radioactive drug is being used under the conditions generally recognized as safe and effective, the Atomic Energy Commission and the Agreement States will use, as one precondition for licensing, notification by the appropriate FDA-approved Radiation Safety Committee that it has approved the proposed study in accordance with Food and Drug Administration regulations. The Food and Drug Administration will provide the Atomic Energy Commission and appropriate State officials with a complete and current list of all FDA-approved Radiation Safety Committees.

In order to notify the Atomic Energy Commission and/or appropriate State officials that an IND has been accepted, however, the Food and Drug Administration needs the consent of the sponsor of the IND. In order to provide a mechanism for obtaining this consent, the Commissioner proposes to amend § 312.1, by adding a new item 16 to Form FD–1571, to request that persons submitting a "Notice of Claimed Investigational Exemption for a New Drug" for a radioactive drug include a summary of the information contained therein and authorization for the Food and Drug Administration to furnish such summary to appropriate Federal and State officials for their use in licensing such persons to possess, use, or transfer the radioactive drug in a particular State or States. The Commissioner also proposes to amend § 312.1, by adding a new item 6.1 to Form FD–1572 and a new item 4.1 to Form FD–1573, to request an investigator to acknowledge in his "Statement of Investigator" that he understands and agrees that the information he submits to the sponsor regarding any radioactive drug may be furnished in a summarized form to appropriate Federal and State officials. The Food and Drug Administration is requesting sponsors and investigators to submit voluntarily such summaries and authorizations. While failure to submit such information would not be grounds for termination of the claimed investigational exemption under § 312.1, the Food and Drug Administration would not be able to furnish verification to the Atomic Energy Commission and the States that a proper IND has been filed. Without such confirmation, licensing cannot be accomplished by Federal and State officials.

F. *Relationships between the Food and Drug Administration and licensing for use of non-reactor-produced materials by all States.* Persons handling accelerator-produced or naturally occurring radionuclides, which are not subject to control by the Atomic Energy Commission, are licensed in various ways by the individual States and localities. Upon request of any State or locality with licensing authority, the Food and Drug Administration will follow the procedures outlined in paragraph E of this preamble in order to assist in licensing persons to handle non-reactor-produced radioactive material in connection with radioactive drug research, diagnosis, therapy, or other medical and scientific research.

Accordingly, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 701(a), 52 Stat. 1052–53, as amended, 1055; 21 U.S.C. 351, 371(a)), and to the provisions of the Public Health Service Act (sec. 351, 58 Stat. 702, as amended; 42 U.S.C. 262), and under authority delegated to him (21 CFR 2.120), and in cooperation with the Atomic Energy Commission, the Commissioner of Food and Drugs proposes to amend Parts 1, 310, 312, and 370 of Title 21 of the Code of Federal Regulations as follows:

PART 1—REGULATIONS FOR THE ENFORCEMENT OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AND THE FAIR PACKAGING AND LABELING ACT

1. In § 1.106 by adding a new paragraph (p) to read as follows:

§ 1.106 Drugs and devices; directions for use.

* * * * *

(p) *Exemption for radiocative drugs for research uses.* A radioactive drug intended for administration to human research subjects during the course of a research project intended to obtain basic research information regarding metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry (but not intended for immediate therapeutic, diagnostic, or similar purposes), under the conditions set forth in § 370.100 of this chapter, shall be exempt from section 502(f)(1) of the act if the packaging, label, and labeling are in compliance with § 370.100(f) of this chapter.

PART 310—NEW DRUGS

2. By amending § 310.503 by revising paragraph (d), and adding new paragraphs (f), (g), and (h), to read as follows:

§ 310.503 Requirements regarding certain radioactive drugs.

* * * * *

(d) (1) In view of the extent of experience with the isotopes listed in paragraph (c) of this section, the Atomic Energy Commission and the Food and Drug Administration conclude that such isotopes should not be distributed under investigational-use labeling when they are actually intended for use in medical practice.

(2) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (c) of this section, in the "chemical form" and intended for the uses stated, is terminated on March 3, 1972, except as provided in paragraph (d)(3) of this section.

(3) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (c) of this section, in the "chemical form" and intended for the uses stated, for which drug a new drug application or a "Notice of Claimed Investigational Exemption for a New Drug" was submitted prior to March 3, 1972, or for which biologic an application for product license or "Notice of Claimed Investigational Exemption for a New Drug" was submitted prior to March 3, 1972, is terminated either upon issuance of a nonapprovable notice for the new drug application or application for product license or termination of the "Notice of Claimed Investigational Exemption for a New Drug," or on July 1, 1975, whichever occurs first.

* * * * *

(f) (1) Based on its experience in regulating investigational radioactive pharmaceuticals, the Atomic Energy Commission has compiled a list of reactor-produced isotopes for which it considers that applicants may reasonably be expected to submit adequate evidence of safety and effectiveness for use as recommended in appropriate labeling; such use may include, among others, the uses in this tabulation:

Isotope	Chemical form	Use
Fluorine 18	Fluoride	Bone imaging.
Technetium 99m	Human serum albumin microspheres.	Lung imaging.
Do	Diethylenetriamine pentaacetic acid (Sn).	Kidney imaging; kidney function studies.
Do	do	Brain imaging.
Do	Polyphosphates	Bone imaging.
Do	Technetated aggregated albumin (human).	Lung imaging.
Do	Disodium etidronate.	Bone imaging.

(2) In view of the extent of experience with the isotopes listed in paragraph (f)(1) of this section, the Atomic Energy Commission and the Food and Drug Administration conclude that they should not be distributed under investigational-use labeling when they are actually intended for use in medical practice.

(3) Any manufacturer or distributor interested in continuing to ship in interstate commerce drugs containing the isotopes listed in paragraph (f)(1) of this section for any of the indications listed, shall submit, on or before December 31, 1974, to the Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852, a new drug application or a "Notice of Claimed Investigational Exemption for a New Drug" for each such drug for which the manufacturer or distributor does not have an approved new drug application pursuant to section 505(b) of the act. If the drug is a biologic, a "Notice of Claimed Investigational Exemption for a New Drug"

or an application for a license under section 351 of the Public Health Service Act shall be submitted to the Bureau of Biologics, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20014, in lieu of any submission to the Bureau of Drugs.

(4) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (f) (1) of this section, in the "chemical form" and intended for the uses stated, is terminated on January 1, 1975, except as provided in paragraph (f) (5) of this section.

(5) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (f) (1) of this section, in the "chemical form" and intended for the uses stated, for which drug a new drug application or a "Notice of Claimed Investigational Exemption for a New Drug" was submitted to the Bureau of Drugs prior to January 1, 1975, or for which biologic an application for product license or "Notice of Claimed Investigational Exemption for a New Drug" was submitted to the Bureau of Biologics prior to January 1, 1975, is terminated either upon issuance of an nonapprovable notice for the new drug application or application for product license or termination of the "Notice of Claimed Investigational Exemption for a New Drug," or on July 1, 1975, whichever occurs first.

(g) The exemption referred to in paragraph (a) of this section, as applied to any drug intended solely for investigational use as part of a research project, which use had been approved on or before October 1, 1974, in accordance with 10 CFR 35.11 (or equivalent regulation of an Agreement State) is terminated on July 1, 1975, if the manufacturer of such drug or the sponsor of the investigation of such drug submits on or before December 31, 1974, to the Food and Drug Administration, Bureau of Drugs, HFD-150, 5600 Fishers Lane, Rockville, MD 20852, the following information:

(1) The research project title;

(2) A brief description of the purpose of the project;

(3) The name of the investigator responsible;

(4) The name and license number of the institution holding the specific license under 10 CFR 35.11 (or equivalent regulation of an Agreement State);

(5) The name and maximum amount per subject of the radionuclide used;

(6) The number of subjects involved; and

(7) The date on which the administration of the radioactive drugs is expected to be completed.

(h) The exemption referred to in paragraph (a), as applied to any drug not referred to in paragraphs (d), (f), and (g) of this section, is terminated on January 1, 1975.

PART 312—NEW DRUGS FOR INVESTIGATIONAL USE

§ 312.1 [Amended]

3. In § 312.1:

a. By amending Form FD-1571 set forth in paragraph (a) (2) by adding a new item 6.d, by adding a flush paragraph to item 10.a, and by adding a new item 16; by amending Form FD-1572 set forth in paragraph (a) (12) by adding a new item 6.i; and by amending Form FD-1573 set forth in paragraph (a) (13) by adding a new item 4.i, as follows:

(a) * * *

(2) * * *

FORM FD-1571

* * * * *

6. * * *

d. If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being.

* * * * *

10. * * *

a. * * *

If a drug is a radioactive drug, the clinical pharmacology phase must include studies which will obtain sufficient data for dosimetry calculations. These studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material.

* * * * *

16. If the drug is a radioactive drug, a summary of information and authorization for release to appropriate Federal, State and local officials shall be included in the following format:

RADIOACTIVE DRUGS FOR INVESTIGATIONAL USE

SUMMARY OF INFORMATION

a. Name and address of the sponsor.

b. Name of the investigational radioactive drug.

c. Description of the investigational radioactive drug including the generic name of the drug, its chemical and physical form, and whether the radioactivity is naturally occurring, artificially produced, or produced by nuclear fission.

d. Names and addresses of all investigators and their affiliated institutions.

e. Purpose of the clinical trial, e.g., diagnostic, therapeutic, etc.

f. Number of subjects to be studied by each investigator and criteria for subject selection by age, sex, and condition, e.g., normal healthy volunteer, sick volunteer, etc.

g. Dosage, i.e., ranges and route of administration.

h. Duration of the clinical investigation.

i. A statement as to whether or not the investigation will be subject to the review of an institutional review committee.

j. A statement that the sponsor authorizes the Food and Drug Administration to release this summary of information, in whole or in part, to appropriate Federal, State, or local officials for their use in licensing persons to possess, handle, or transfer the investigational radioactive drug in a particular state or locality.

(Sponsor)

Per_____

(Indicate Authority)

NOTE: This summary, if released by the Food and Drug Administration to appropriate Federal, State, or local officials, will have attached to it by the Food and Drug Administration the number of the claimed investigational exemption, the date of receipt of the claimed investigational exemption by the Food and Drug Administration, and a statement as to whether the Food and Drug Administration has requested the sponsor to continue to withhold or to restrict use of the drug in human subjects after the expiration of the 30-day interval provided for in § 312.1 (a) (2) of Title 21 of the Code of Federal Regulations.

* * * * *

(12) * * *

FORM FD 1572

* * * * *

6. * * *

i. The investigator understands and agrees that the information submitted by him to the sponsor regarding any radioactive drug may be furnished in a summarized form to appropriate Federal, State, and local officials for their use in licensing persons to possess, handle, or transfer the radioactive drug in a particular state or locality.

* * * * *

(13) * * *

FORM FD 1573

* * * * *

4. * * *

i. The investigator understands and agrees that the information submitted by him to the sponsor regarding any radioactive drug may be furnished in a summarized form to appropriate Federal, State, and local officials for their use in licensing persons to possess, handle, or transfer the radioactive drug in a particular state or locality.

* * * * *

b. By deleting in its entirety, effective January 1, 1975, the "Note" regarding an order of the Commissioner of Food and Drugs published in the FEDERAL REGISTER on January 8, 1963 (28 FR 183), as it appears at the end of § 312.1.

PART 370—PRESCRIPTION HUMAN DRUGS GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

4. By adding a new Part 370, to consist at this time of the following:

SUBPART A—DEFINITIONS AND PROCEDURES [RESERVED]

SUBPART B—DRUG MONOGRAPHS

Sec.

370.100 Radioactive drugs for certain research uses.

AUTHORITY: Federal Food, Drug, and Cosmetic Act, Sec. 505, 701(a), 52 Stat. 1052-53, as amended, 1055; (21 U.S.C. 355, 371(a); Public Health Service Act, Sec. 351, 58 Stat. 702, as amended, (42 U.S.C. 262); 21 CFR 2.120.

Subpart A—Definitions and Procedures [Reserved]

Subpart B—Drug Monographs

§ 370.100 Radioactive drugs for certain research uses.

(a) Radioactive drugs are generally recognized as safe and effective when administered, under the conditions set

forth in paragraph (b) of this section, to human research subjects during the course of a research project intended to obtain basic research information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes. Certain basic research studies, e.g., studies to determine whether a drug localizes in a particular organ or fluid space and to describe the kinetics of that localization, may have eventual therapeutic or diagnostic implications, but the initial studies are considered to be basic research within the meaning of this section.

(b) The conditions under which use of radioactive drugs for research are considered safe and effective are:

(1) *Approval by Radiation Safety Committee.* A Radiation Safety Committee, composed and approved by the Food and Drug Administration in accordance with paragraph (c) of this section, has determined, in accordance with the standards set forth in paragraph (d) of this section, that:

(i) The pharmaceutical dose is within the limits set forth in paragraph (b) (2) of this section;

(ii) The radiation dose is within the limits set forth in paragraph (b) (3) of this section;

(iii) The radiation exposure is justified by the quality of the study being undertaken and the importance of the information it seeks to obtain;

(iv) The study meets the other requirements set forth in paragraph (d) of this section regarding qualifications of the investigator, proper licensure for handling radioactive materials, selection and consent of research subjects, quality of radioactive drugs used, research protocol design, reporting of adverse reactions, and approval by an appropriate Institutional Review Committee; and

(v) The use of the radioactive drug in human subjects has the approval of the Radiation Safety Committee.

(2) *Limit on pharmaceutical dose.* The amount of active pharmaceutical ingredient or combination of active pharmaceutical ingredients to be administered shall be known not to cause any clinically detectable pharmacological effect in human beings.

(3) *Limit on radioactive dose.* The amount of radioactive material to be administered shall be such that the subject is exposed to the smallest amount of radioactivity with which it is practical to perform the study without jeopardizing the quality of the study. In no circumstances, however, may the amount exceed any of the currently permitted occupational exposure limitations for the radionuclide under the most analogous conditions. For whole body exposure for adult research subjects, the maximum permissible limitations are as follows:

	Rem
Single exposure	3
Quarterly cumulative	3
Yearly cumulative	5

For critical organ exposure for adult research subjects, the maximum permissible limitations are as follows:

	Rem
Single exposure	5
Quarterly cumulative	5
Yearly cumulative	15

For a research subject under 18 years of age at his last birthday, the maximum permissible whole body and critical organ exposure limitations are 10 percent of the foregoing. Numerical definitions of exposure shall be based on an absorbed fraction method of radiation absorbed dose calculation, such as the system set forth by the Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine, or the system set forth by the International Committee of Radiation Protection.

(c) A Radiation Safety Committee, in order to comply with paragraph (b) (1) of this section, shall be composed, shall function, and shall obtain and maintain approval of the Food and Drug Administration in conformity with the following:

(1) *Membership.* A Radiation Safety Committee shall consist of at least five individuals qualified in varied disciplines pertinent to the field of nuclear medicine (e.g., radiology, internal medicine, clinical pathology, hematology, endocrinology, radiation therapy, radiation physics, radiation biophysics, health physics, and radiopharmacy), including a physician recognized as a specialist in nuclear medicine, a person qualified by training and experience to formulate radioactive drugs, and other persons with special competence in radiation safety and radiation dosimetry. Membership shall be sufficiently diverse to permit expert review of the technical and scientific aspects of proposals submitted to the committee. The addition of consultants in other pertinent medical disciplines is encouraged. A Radiation Safety Committee shall be either associated with a medical institution operated for care of patients and with sufficient scientific expertise to allow for selection of committee members from its faculty, or with a committee established by a State authority to provide advice on radiation health matters. Joint committees involving more than one medical institution which have been established in order to achieve a high level and diversity of experience will be acceptable. The Director of the Bureau of Drugs may modify any of the foregoing requirements in a particular situation where alternative factors provide substantially the same composition and association.

(2) *Function.* Each Radiation Safety Committee shall select a chairman, who shall sign all applications, minutes, and reports of the committee. Each committee shall meet at least quarterly with a quorum present. Minutes shall be kept and shall include the numerical results of votes on protocols involving use in human subjects. No member shall vote on a protocol in which he is an investigator.

(3) *Reports.* Each Radiation Safety Committee shall submit an annual report on or before January 31 of each year to the Food and Drug Administration, Bureau of Drugs, HFD–150, 5600 Fishers Lane, Rockville, MD 20852. The annual report shall include the names and qualifications of the members of, and of any consultants used by, the Radiation Safety Committee, and, for each study conducted during the preceding year, a summary of information presented in the following format:

REPORT ON RESEARCH USE OF RADIOACTIVE DRUG

1. Title of the research project.
2. Brief description of the purpose of the research project.
3. Name of the investigator responsible.
4. Pharmacologic dose:
   a. Active ingredients.
   b. Maximum amount administered per subject.
5. Radiation absorbed dose:
   a. Name of the radionuclide used.
   b. Maximum amount of radioactivity administered per subject.
   c. Maximum cumulative radiation exposure per subject.
   d. Single radiation exposure per subject.
6. Number of subjects used.
7. A claim of confidentiality, if any.

NOTE: Contents of this report, except for information regarding the name of the investigator, are available for public disclosure unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential information because it is unique, has not previously been disclosed in an authorized manner to anyone other than a company employee or paid consultant, has been developed at significant cost, and provides a competitive advantage.

Investigator

Chairman, Radiation Safety Committee

At any time a proposal is approved which will result in exposure either of more than 30 research subjects, or of any research subject under 18 years of age, the committee shall immediately submit to the Food and Drug Adminstration a special summary of information in the format shown, except that item 6 shall include the ages of the subjects, if relevant. Contents of these reports, except for information regarding the name of the investigator, are available for public disclosure, unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential information because it is unique, has not previously been disclosed in an authorized manner to anyone other than a company employee or paid consultant, has been developed at significant cost, and provides a competitive advantage.

(4) *Approval.* Each Radiation Safety Committee shall be specifically approved by the Bureau of Drugs of the Food and Drug Administration. Applications shall be submitted to the Food and Drug Administration, Bureau of Drugs, HFD–150, 5600 Fishers Lane, Rockville, MD 20852, and shall contain the names and qualifications of the members of the committee, and a statement that the committee agrees to comply with the requirements set forth in this section. Approval shall be based upon an assessment of the

qualifications of the members of the committee, and the assurance that all necessary fields of expertise are covered. Approval of a committee may be withdrawn at any time for failure of the committee to comply with any of the requirements of this section.

(5) *Monitoring.* The Food and Drug Administration shall conduct periodic reviews of approved committees. Monitoring of the activities of the committee shall be conducted through review of its annual report, through review of minutes and full protocols for certain studies, and through on-site inspections.

(d) In making the determinations required in paragraph (b)(1) of this section, a Radiation Safety Committee shall consider the following requirements and assure that each is met:

(1) *Radiation exposure per subject.* In order to determine that radiation exposure does not exceed limitations set forth in paragraph (b)(3) of this section, the Radiation Safety Committee shall require that the investigator provide absorbed dose calculations based on biologic distribution data available from published literature or from other valid studies. Under no circumstances may an individual human subject, through repeated study, receive an absorbed dose of radiation exceeding that permissible for occupationally exposed personnel.

(2) *Pharmacological dosage.* In order to determine that the amount of active pharmaceutical ingredients to be administered does not exceed the limitations set forth in paragraph (b)(2) of this section, the committee shall require that the investigator provide pharmacological dose calculations based on data available from published literature or from other valid human studies.

(3) *Qualifications of investigators.* Each investigator shall be qualified by training and experience to conduct the proposed research studies.

(4) *License to handle radioactive materials.* The responsible investigator or institutions shall, in the case of reactor-produced isotopes, be licensed by the Atomic Energy Commission or Agreement State to possess and use the specific radionuclides for research use or be a listed investigator under a broad license, or in the case of non-reactor-produced isotopes, be licensed by other appropriate State or local authorities, when required by State or local law, to possess and use the specific radionuclides for research use.

(5) *Human research subjects.* Each investigator shall select appropriate human subjects and shall obtain the consent of such human beings or their representatives in accordance with § 310.102 of this chapter. The research subjects shall be at least 18 years of age and legally competent. Exceptions are permitted only in those special situation when it can be demonstrated to the committee that the study presents a unique opportunity to gain information not presently available and requires the use of research subjects less than 18 years of age and is without significant risk to the subject. Studies involving minors shall be supported with review by qualified pediatric consultants to the Radiation Safety Committee. Each female research subject of child-bearing potential shall state in writing that she is not pregnant, or be given a pregnancy test, before she may participate in any study.

(6) *Quality of radioactive drug.* The radioactive drug used in the research study shall be of appropriate standards of identity, strength, quality, and purity (chemical, pharmaceutical, radiochemical, and radionuclidic) as needed for safety and be of such uniform and reproducible quality as to give significance to the research study conducted. The Radiation Safety Committee shall determine that radioactive materials for parenteral use are available in sterile and pyrogen-free form.

(7) *Research protocol.* No study involving administration of radioactivity to research subjects, no matter how small the amount of radioactivity, shall be permitted unless the Radiation Safety Committee concludes, in its judgment, that scientific knowledge and benefit is likely to result from that study. Therefore, the protocol shall be based upon a sound rationale derived from appropriate animal studies or published literature and shall be of sound design such that information of scientific value may result. The radiation dose shall be both sufficient and no greater than necessary to obtain valid measurement. The projected number of subjects shall be sufficient but no greater than necessary for the purpose of the study. The number of subjects shall also reflect the fact that the study is intended to obtain basic research information referred to in paragraph (a) of this section and no intended for immediate therapeutic, diagnostic or similar purposes.

(8) *Adverse reactions.* The investigator shall immediately report to the Radiation Safety Committee all adverse effects associated with the use of the radioactive drug in the research study. All adverse reactions probably attributable to the use of the radioactive drug in the research study shall be immediately reported by the Radiation Safety Committee to the Food and Drug Administration, Bureau of Drugs, HFD–150, 5600 Fishers Lane, Rockville, MD 20852.

(9) *Approval by Institutional Review Committee.* The investigator shall obtain the review and approval of an Institutional Review Committee which conforms to "The Institutional Guide to DHEW Policy on Protection of Human Subjects," National Institutes of Health, DHEW Publication No. (NIH) 72–102. A codified version of the DHEW guide was published in the FEDERAL REGISTER of May 30, 1974 (39 FR 18914) under 45 CFR Part 46 *Protection of Human Subjects.*[1]

(e) The results of any research conducted pursuant to this section as part of the evaluation of a drug pursuant to § 312.1 of this chapter shall be included in the submission required under § 312.1 of this chapter.

(f) A radioactive drug prepared, packaged, distributed, and primarily intended for use in the accordance with the requirements of this section shall be exempt from section 502(f)(1) of the act and § 1.106 of this chapter if the packaging, label, and labeling are in compliance with Federal, State, and local law regarding radioactive materials and if the label and labeling either separate from or as part of any label and labeling required for radioactive materials by the Atomic Energy Commission or by State or local radiological health authorities bear the following:

(1) The statement "Caution: Federal law prohibits dispensing without prescription";

(2) The statement "To be administered in compliance with the requirements of Federal regulations regarding radioactive drugs for research use (21 CFR 370.100)";

(3) The name, quantity, and half-life of the radionuclide;

(4) An identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug; and

(5) If the drug is intended for parenteral use, a statement as to whether the contents are sterile.

Interested persons are invited to submit their comments in writing (preferably in quintuplicate) regarding this proposal on or before September 27, 1974. Such comments should be addressed to the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, and may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: July 23, 1974.

SHERWIN GARDNER,
Deputy Commissioner of Food and Drugs.

[FR Doc.74–17223 Filed 7–26–74;8:45 am]

[1] Copies may be obtained from: National Institutes of Health, Division of Research Grants, Westwood Bldg., Rm. 448, 5333 Westbard Ave., Bethesda, MD 20016.

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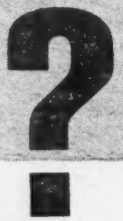

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